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Review

Moyamoya Disease: Physiological Mechanisms and Treatment Approaches

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Abstract: Moyamoya disease (MMD) is a rare, progressive cerebrovascular disorder marked by stenosis of the terminal internal carotid arteries and the formation of fragile collateral vessels, leading to reduced cerebral perfusion and heightened risks of ischemic and hemorrhagic strokes. Its pathophysiology involves endothelial dysfunction, aberrant angiogenesis, and genetic mutations, notably in the RNF213 gene. This paper examines normal cerebrovascular physiology, the pathological changes driving MMD, its clinical features, and current therapeutic approaches. Treatments, including medical management and surgical revascularization (e.g., direct and indirect bypass), aim to restore cerebral blood flow and mitigate stroke risk, with revascularization proving most effective. Elucidating the physiological underpinnings of MMD is vital for developing targeted therapies and enhancing patient outcomes.

Acronyms and Keywords: ACTA2 (Gene associated with Moyamoya Disease); CBF (Cerebral Blood Flow); EDAS (Encephalon-Duro-Arterio-Synangiosis); ET-1 (Endothelin-1); GUCY1A3 (Gene associated with Moyamoya Disease); MMD (Moyamoya Disease); MRA (Magnetic Resonance Angiography); MRI (Magnetic Resonance Imaging); NO (Nitric Oxide); PaCO2 (Arterial Carbon Dioxide); RNF213 (Gene associated with Moyamoya Disease); SPECT (Single-Photon Emission Computed Tomography); TCD (Transcranial Doppler); TIA (Transient Ischemic Attack)

Introduction

Moyamoya disease (MMD), a rare and progressive cerebrovascular disorder, predominantly affects children and young adults, though its reach spans all ages (1). Named from the Japanese term for "puff of smoke," MMD is characterized by the stenosis of terminal internal carotid arteries and the emergence of fragile collateral vessels that resemble wispy clouds on angiography. This compensatory network, while a testament to the brain's resilience, often fails, leading to chronic cerebral hypoperfusion and a heightened risk of ischemic and hemorrhagic strokes—devastating outcomes that can rob patients of motor function, cognition, or life itself. Though its pathogenesis remains elusive, genetic mutations like RNF213, prevalent in East Asian populations, hint at a complex interplay of hereditary and environmental triggers. Despite its rarity, MMD's impact is profound, necessitating urgent advances in diagnosis and care. Treatment strategies, from medical management to sophisticated surgical revascularization, aim to restore blood flow and avert neurological decline, yet challenges persist. This paper explores MMD comprehensively: from the normal physiology of cerebral blood flow and its disruption in MMD, through its genetic and hemodynamic underpinnings, to its clinical presentation, diagnostic approaches, and evolving therapies. By illuminating these facets, we seek to enhance understanding and guide the development of targeted interventions for improved patient outcomes.

Normal Physiology of Cerebral Blood Flow Regulation

The brain's vascular system is a specialized network that ensures a continuous supply of oxygen and nutrients for neuronal function. The internal carotid and vertebral arteries, key conduits of this system, converge at the brain's base to form the Circle of Willis—an arterial ring composed of the

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anterior and posterior cerebral arteries. This structure enables collateral blood flow, allowing blood to bypass blockages or narrowing in major arteries, thus protecting against ischemic events like strokes and maintaining stable perfusion across both hemispheres (2). Beyond nutrient delivery, the Circle of Willis may also regulate cerebral pressure and maintain intracranial homeostasis. In Moyamoya disease (MMD), however, narrowing or occlusion of these arteries triggers the formation of fragile collateral vessels, which often fail to compensate adequately, leading to ischemic or hemorrhagic complications. This vulnerability highlights the critical role of the cerebral arterial network in sustaining circulation.

Cerebral blood flow (CBF) is tightly regulated to deliver a consistent supply of oxygen and nutrients despite fluctuations in systemic blood pressure. This autoregulation relies on multiple mechanisms. The myogenic response enables cerebral arteries to constrict or dilate in response to changes in intraluminal pressure, stabilizing CBF. Metabolic regulation, meanwhile, adjusts blood flow to meet local neuronal demands; increased activity releases vasodilators like adenosine and nitric oxide (NO), enhancing CBF in active regions. Though less dominant, the autonomic nervous system, particularly sympathetic innervation, also modulates CBF.

Additionally, CBF responds to changes in arterial carbon dioxide (PaCO2) and pH: hypercapnia (elevated PaCO2) and acidosis induce vasodilation, while hypocapnia (reduced PaCO2) and alkalosis cause vasoconstriction (3). The endothelium further regulates CBF by releasing vasoactive substances, such as NO, a potent vasodilator, and endothelin-1 (ET-1), a vasoconstrictor. The balance between these factors is essential for maintaining vascular tone and optimal CBF (4).

Pathophysiology of Moyamoya Disease

The defining feature of Moyamoya disease (MMD) is the relentless, progressive stenosis and eventual occlusion of the distal internal carotid arteries and the proximal segments of the anterior and middle cerebral arteries, a process that severely compromises cerebral blood flow (CBF) to critical brain regions. In a desperate bid to counter this hypoperfusion, the brain triggers the formation of an intricate yet frail network of collateral vessels—aptly likened to a "puff of smoke" on angiography—though these compensatory channels, with their thin-walled, poorly organized structure, are notoriously unstable, predisposing them to rupture or thrombosis. The etiology of MMD remains incompletely understood, shrouded in a complex interplay of genetic predisposition and environmental influences. Central to its pathogenesis are genetic mutations, with the RNF213 gene emerging as a pivotal player, particularly in East Asian populations where its prevalence reaches up to 90% in familial cases (5). RNF213 disrupts vascular stability by impairing endothelial cell function and promoting aberrant angiogenesis, potentially through heightened inflammation or oxidative stress. Other implicated genes, such as ACTA2 and GUCY1A3, further underscore the hereditary basis of this disorder, altering smooth muscle integrity and guanylate cyclase signaling, which compromise vascular resilience (5). Environmental triggers, such as chronic inflammation or autoimmune processes, may amplify these genetic vulnerabilities, accelerating disease progression.

The stenotic occlusion of major cerebral arteries precipitates a marked reduction in CBF—often dropping below 30 mL/100g/min in affected regions—while crippling cerebrovascular reserve, the brain's capacity to dilate vessels in response to heightened metabolic demand or stress (6). This impaired autoregulation, compounded by endothelial dysfunction, leaves the brain exquisitely susceptible to ischemic insults. Endothelial cells in MMD exhibit reduced nitric oxide (NO) production—a key vasodilator—coupled with elevated endothelin-1 (ET-1), tilting the balance toward vasoconstriction and exacerbating hypoperfusion (4). The fragile collaterals, meanwhile, pose a dual threat: thrombosis can precipitate ischemic strokes, abruptly starving brain tissue of oxygen, while their rupture, driven by hemodynamic stress on weakened vessel walls, can unleash devastating hemorrhagic strokes, flooding the intracranial space with blood. Although MMD predominantly ravages the cerebral vasculature, its ripple effects extend systemically; chronic hypoperfusion erodes cognitive faculties, manifesting as memory deficits, executive dysfunction, and slowed processing speed, and undermines overall neurological function, profoundly impacting quality of life. These multifaceted consequences highlight the urgent need to unravel MMD's physiological and molecular underpinnings to devise more effective therapeutic strategies.

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Clinical Signs and Symptoms

Moyamoya disease (MMD) manifests through a spectrum of neurological symptoms driven by cerebral hypoperfusion and collateral vessel instability. Brief episodes of neurological dysfunction, such as unilateral weakness (hemiparesis), numbness, aphasia, or visual disturbances—termed transient ischemic attacks (TIAs)—typically resolve within minutes to hours and may be triggered by hyperventilation or dehydration, which exacerbate vasoconstriction. Sudden ischemic strokes, occurring in 50-75% of untreated patients, can cause permanent deficits like hemiplegia or speech impairment, reflecting occlusion of the middle cerebral artery territory. Seizures, arising from ischemia or cortical scarring, affect a subset of patients, while chronic hypoperfusion leads to cognitive deficits—memory loss, executive dysfunction, and slowed processing speed—sometimes accompanied by irritability or depression due to frontal lobe involvement. Hemorrhagic events, more common in adults (up to 40% in East Asian cohorts), result from fragile collateral vessel rupture, causing intracerebral or subarachnoid hemorrhage with severe headaches, neck stiffness, or unconsciousness. Chronic headaches, possibly from vascular anomalies, are frequent across all ages. In children, developmental delays or rare choreiform movements signal chronic ischemia, contrasting with adults' hemorrhagic predominance. These symptoms stem from progressive arterial stenosis, reducing cerebral blood flow (CBF) and the fragility of compensatory collaterals. Ischemic events arise from thrombosis or critically low perfusion, while hemorrhages reflect hemodynamic stress on weakened vessels. Symptom severity and type depend on the location and extent of affected brain tissue, with untreated cases progressing from transient to permanent deficits.

Diagnosis

Diagnosing Moyamoya disease (MMD) relies on a multimodal imaging approach to confirm progressive stenosis of the terminal internal carotid arteries (ICAs), visualize compensatory collateral networks, and assess cerebral perfusion deficits. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) serve as initial, non-invasive cornerstones. MRI detects ischemic infarcts, white matter lesions, or hemorrhagic sequelae in brain parenchyma, often revealing silent strokes in asymptomatic patients. MRA delineates the characteristic narrowing or occlusion of the distal ICAs and proximal anterior/middle cerebral arteries, alongside the hazy, cloud-like "Moyamoya" collaterals—lenticulostriate or thalamo-perforating vessels—that define the disease's angiographic signature. Time-of-flight MRA, commonly used, offers high sensitivity for detecting these vascular anomalies without contrast, though its resolution may miss subtle collateral networks (10). Cerebral angiography remains the gold standard, providing unparalleled detail of the cerebral vasculature. This invasive technique maps the extent of ICA stenosis, quantifies collateral vessel proliferation, and enables staging via the Suzuki classification (stages I-VI), which tracks disease progression from mild narrowing to extensive collateral dependence and ICA occlusion (2). The "puff of smoke" appearance—most striking in advanced stages—arises from dilated perforating arteries compensating for reduced flow, a finding critical for distinguishing MMD from mimics like atherosclerosis or vasculitis. Despite its precision, angiography carries risks (e.g., stroke from catheter manipulation), prompting its use primarily for confirmation or preoperative planning (8).

Functional imaging complements structural assessments. Single-photon emission Computed Tomography (SPECT), often paired with acetazolamide challenge, quantifies cerebral blood flow (CBF) and cerebrovascular reserve, identifying ischemic regions at risk of infarction. Hypoperfused areas (CBF <30 mL/100 g/min) correlate with clinical symptoms like TIAs and guide surgical candidacy (6). Transcranial Doppler (TCD) ultrasonography, a non-invasive tool, measures CBF velocity in major arteries and assesses autoregulatory capacity; diminished velocity or reactivity to CO_2 changes signals impaired hemodynamics. While less specific than SPECT, TCD's portability suits serial monitoring. Diagnosis hinges on integrating these findings with clinical presentation—TIAs, strokes, or seizures in children; hemorrhages in adults—while excluding secondary causes (e.g., sickle cell disease, radiation injury). Advanced cases may show ivy signs on MRI (leptomeningeal collaterals) or flow voids in the basal ganglia, further supporting MMD. Collectively, these tools not only confirm the diagnosis but also stratify disease severity, informing prognosis and therapeutic strategies like revascularization.

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Treatment Strategies

The management of Moyamoya disease (MMD) encompasses both medical and surgical approaches, tailored to disease stage, patient age, and clinical presentation (ischemic vs. hemorrhagic). These strategies aim to mitigate cerebral hypoperfusion, prevent stroke, and preserve neurological function by addressing the dual threats of thromboembolism and fragile collateral vessel rupture, guided by advanced imaging to assess revascularization needs (10).

Medical therapy serves as an adjunct to surgical intervention or a temporizing measure for patients unsuitable for surgery. Antiplatelet Therapy, such as aspirin (typically 81-325 mg daily), reduces the risk of thromboembolic events by inhibiting platelet aggregation in stenosed vessels and fragile collaterals, a critical consideration given the high incidence of ischemic strokes (50-75% in untreated cases) (6). Evidence suggests modest efficacy in preventing TIA recurrence, though it does not halt disease progression (2). Calcium Channel Blockers (e.g., nimodipine or nicardipine) are employed to prevent vasospasm and enhance cerebral blood flow (CBF) by relaxing vascular smooth muscle, particularly in patients with symptomatic vasoconstriction triggered by hyperventilation or dehydration (9). These agents may also alleviate chronic headaches, a frequent MMD symptom. Control of Cardiovascular Risk Factors—hypertension, diabetes, and hyperlipidemia—is essential to minimize additional vascular stress, with blood pressure targets often set below 130/80 mmHg to balance perfusion needs and hemorrhage risk (2). Despite these measures, medical management alone fails to address the underlying progressive stenosis, underscoring the primacy of surgical intervention.

Surgical revascularization is the cornerstone of MMD treatment, proven to restore CBF, reduce stroke risk, and improve long-term outcome. Imagingg modalities like MRI and SPECTguideg patient selection and postoperative assessment (10). Techniques fall into three categories: direct, indirect, and combined bypass, each leveraging distinct mechanisms to bypass occluded arteries and bolster cerebral perfusion.

Direct Bypass, exemplified by superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis, establishes an immediate extracranial-to-intracranial conduit (10). A branch of the external carotid artery (e.g., STA) is meticulously sutured to a cortical branch of the middle cerebral artery, bypassing the stenosed internal carotid artery (ICA) (9). The procedure delivers instantaneous CBF augmentation—often increasing from <30 mL/100 g/min to >50 mL/100 g/min in affected regions—making it particularly effective for patients with acute ischemic symptoms or poor cerebrovascular reserve (6). Success hinges on meticulous microsurgical technique and donor-recipient vessel patency, with patency rates exceeding 90% in experienced centers (1). However, it carries perioperative risks, including hyperperfusion syndrome (5-10% incidence), which can precipitate transient neurological deficits or hemorrhage (6).

Indirect Bypass: Indirect methods, such as encephaloduroarteriosynangiosis (EDAS), encephalomyosynangiosis (EMS), or dural inversion, promote angiogenesis by placing vascularized tissue (e.g., temporalis muscle or pericranium) onto the brain surface (10, 8). Over weeks to months, this stimulates collateral vessel formation from extracranial sources, gradually increasing CBF (9). EDAS, the most widely used, leverages the STA without direct anastomosis, making it technically more straightforward and safer for pediatric patients or those with small-caliber vessels (9). Efficacy varies, with angiogenesis success rates ranging from 60-80%, influenced by factors like patient age (higher in children) and RNF213 mutation status (8). While slower to effect, indirect bypass reduces perioperative risks and suits early-stage or asymptomatic cases.

Combined Bypass: Integrating direct and indirect techniques, combined bypass maximizes revascularization by pairing immediate flow (via STA-MCA) with long-term collateral growth (via EDAS or similar) (10). This approach is increasingly favored for advanced MMD (Suzuki stages IV-VI), where extensive collateral dependence and profound hypoperfusion demand robust intervention (11). Studies report superior stroke-free survival rates—up to 95% at 5 years—compared to single-technique strategies, though it requires excellent surgical expertise and longer operative time (12).

Surgical candidacy hinges on imaging evidence of compromised CBF (e.g., SPECT showing <30 mL/100 g/min) and clinical factors like recurrent TIAs or strokes (10). Direct bypass excels in adults

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with acute ischemia, while indirect methods dominate in children due to their robust angiogenic potential (13). Combined approaches bridge these benefits, though comparative trials remain limited (14).

Beyond established methods, experimental approaches are gaining traction. Gene Therapy targeting RNF213 or angiogenesis pathways (e.g., VEGF upregulation) aims to correct endothelial dysfunction and enhance collateral stability, though human trials are nascent (15). Stem Cell Therapy, using mesenchymal stem cells to promote vascular repair, shows promise in preclinical models by boosting NO production and reducing inflammation (13). Pharmacological agents like cilostazol, a phosphodiesterase inhibitor, are under investigation for their dual antiplatelet and vasodilatory effects, potentially augmenting CBF more effectively than aspirin alone (12). These innovations, while preliminary, signal a shift toward personalized, molecularly targeted MMD management.

Treatment selection balances efficacy, risk, and patient factors, with imaging playing a pivotal role in planning and follow-up (16). Direct bypass offers rapid relief but demands surgical precision; indirect bypass prioritizes safety and long-term gains; combined bypass optimizes outcomes at higher complexity. Postoperative care includes antiplatelet continuation, CBF monitoring via TCD or SPECT, and managing hyperperfusion risks with strict blood pressure control (e.g., systolic 100-140 mmHg) (16). Multidisciplinary teams—neurosurgeons, neurologists, and rehabilitation specialists—ensure holistic care, addressing both vascular and neurological sequelae.

Prognosis and Long-Term Management

Physiologically, MMD's prognosis hinges on the brain's ability to adapt to chronic hypoperfusion and the success of interventions in re-establishing hemodynamic stability. Pre-treatment, the stenotic ICAs impair autoregulation—the myogenic and metabolic mechanisms that usually stabilize CBF despite systemic pressure fluctuations (see Normal Physiology of Cerebral Blood Flow Regulation). This forces reliance on fragile collateral vessels, prone to thrombosis or rupture with their thin-walled, disorganized structure (17). Successful revascularization, whether direct (e.g., STA-MCA bypass) or indirect (e.g., EDAS), reintroduces extracranial blood flow, elevating regional CBF and partially restoring autoregulatory capacity (17). For instance, direct bypass can boost CBF from <30 mL/100 g/min to >50 mL/100 g/min acutely, alleviating ischemic stress (17). However, this sudden hemodynamic shift risks hyperperfusion syndrome (5-10% incidence), where excessive flow overwhelms previously hypoperfused tissue, triggering edema or hemorrhage due to disrupted endothelial integrity and elevated endothelin-1 (ET-1) levels (17). In the long term, the balance between nitric oxide (NO)-mediated vasodilation and ET-1-induced vasoconstriction must stabilize to sustain vascular tone and prevent such complications (14).

Effective long-term management integrates regular physiological monitoring with tailored interventions. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) track disease progression and bypass patency, assessing whether CBF remains above ischemic thresholds (17). Single-photon emission Computed Tomography (SPECT) with acetazolamide challenge quantifies cerebrovascular reserve, revealing regions at risk if autoregulation falters (16). Transcranial Doppler (TCD) provides real-time CBF velocity data, guiding adjustments in antiplatelet therapy (e.g., aspirin) or blood pressure control (target systolic 100-140 mmHg) to prevent thromboembolism or hyperperfusion (18). For hemorrhagic-prone patients, managing collateral vessel stability is critical; excessive hemodynamic stress on these vessels, exacerbated by hypertension or $PaCO_2$ fluctuations, can precipitate rupture, necessitating strict $PaCO_2$ homeostasis via controlled ventilation or lifestyle adjustments (19). Emerging therapies, like cilostazol, aim to enhance NO production and vasodilation, potentially offering a dual protective effect against ischemia and vascular instability (19).

Conclusions

Moyamoya disease (MMD) is a formidable challenge in cerebrovascular medicine, defined by its progressive stenosis of the internal carotid arteries and the precarious formation of fragile collateral vessels. This paper has elucidated the intricate interplay between normal cerebral blood flow (CBF) regulation— reliant on autoregulatory mechanisms like myogenic responses and nitric oxide (NO)-mediated vasodilation—and its disruption in MMD, where endothelial dysfunction, genetic mutations (notably RNF213), and aberrant angiogenesis precipitate chronic hypoperfusion and vascular instability. These physiological disruptions manifest clinically as transient ischemic attacks, debilitating strokes, cognitive decline, and hemorrhagic events, underscoring the disease's profound impact on patients across age groups. Current diagnostic tools, from MRI/MRA to cerebral angiography and SPECT, enable precise visualization of these vascular anomalies and guide therapeutic decision-making, while treatment strategies—spanning medical management with antiplatelets and surgical revascularization via direct, indirect, or combined bypass—offer critical avenues to restore CBF and mitigate stroke risk.

Surgical revascularization, in particular, emerges as a cornerstone of MMD management, with techniques like STA-MCA bypass and EDAS demonstrably improving hemodynamic stability and long-term outcomes, evidenced by stroke-free survival rates reaching up to 95% at five years in advanced cases. Yet, the disease's complexity demands more than current solutions can fully address. The persistent risks of hyperperfusion syndrome, the variable efficacy of indirect bypass, and the incomplete understanding of MMD's genetic and environmental triggers highlight significant gaps in knowledge and practice. Moreover, the systemic ripple effects of chronic hypoperfusion—cognitive impairment, developmental delays in children, and reduced quality of life—emphasize the need for holistic, multidisciplinary care beyond vascular correction.

Unraveling the molecular underpinnings of MMD, such as the role of RNF213 in endothelial dysfunction or the potential of genes like ACTA2 and GUCY1A3 as therapeutic targets, is imperative for shifting from symptomatic management to disease-modifying interventions. Emerging approaches, including gene therapy to enhance vascular stability, stem cell therapy to promote repair, and pharmacological agents like cilostazol to bolster CBF, hold promise but require rigorous clinical validation. Enhanced genetic screening, particularly in high-prevalence populations like East Asians, could refine risk stratification and personalize treatment. Ultimately, advancing MMD care hinges on bridging these scientific and clinical frontiers through collaborative research, innovative trials, and a deeper grasp of its physiological roots. By doing so, we can transform the prognosis of this enigmatic disorder, offering patients not just survival, but sustained neurological health and improved quality of life.

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